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Systematic review and meta-analysis of endoscopic submucosal dissection versus transanal endoscopic microsurgery for large noninvasive rectal lesions

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Abstract

Background For almost 30 years, transanal endoscopic microsurgery (TEM) has been the mainstay treatment for large rectal lesions. With the advent of endoscopic submucosal dissection (ESD), flexible endoscopy has aimed at en bloc R0 resection of superficial lesions of the digestive tract. This systematic review and meta-analysis compared the safety and effectiveness of ESD and full-thickness rectal wall excision by TEM in the treatment of large nonpedunculated rectal lesions preoperatively assessed as noninvasive.

Methods A systematic review of the literature published between 1984 and 2010 was conducted (Registration no. CRD42012001882). Data were integrated with those from the original databases requested from the study authors when needed. Pooled estimates of the proportions of patients with en bloc R0 resection, complications, recurrence, and need for further treatment in the ESD and TEM series were compared using random-effects single-arm meta-analysis.

Results This review included 11 ESD and 10 TEM series (2,077 patients). The en bloc resection rate was 87.8 % (95 % confidence interval [CI] 84.3–90.6) for the ESD patients versus 98.7 % (95 % CI 97.4–99.3 %) for the TEM patients ($P < 0.001$). The R0 resection rate was 74.6 % (95 % CI 70.4–78.4 %) for the ESD patients versus 88.5 % (95 % CI 85.9–90.6 %) for the TEM patients ($P < 0.001$). The postoperative complications rate was 8.0 % (95 %, CI

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5.4–11.8 %) for the ESD patients versus 8.4 % (95 % CI 5.2–13.4 %) for the TEM patients ($P = 0.874$). The recurrence rate was 2.6 % (95 % CI 1.3–5.2 %) for the ESD patients versus 5.2 % (95 % CI 4.0–6.9 %) for the TEM patients ($P < 0.001$). Nevertheless, the rate for the overall need of further abdominal treatment, defined as any type of surgery performed through an abdominal access, including both complications and pathology indications, was 8.4 % (95 % CI 4.9–13.9 %) for the ESD patients versus 1.8 % (95 % CI 0.8–3.7 %) for the TEM patients ($P < 0.001$).
Conclusions The ESD procedure appears to be a safe technique, but TEM achieves a higher R0 resection rate when performed in full-thickness fashion, significantly reducing the need for further abdominal treatment.

Keywords Rectal adenoma · Transanal endoscopic microsurgery · Endoscopic submucosal dissection · Systematic review · Meta-analysis

For nearly 30 years, transanal endoscopic microsurgery (TEM) has been the optimal mainstay treatment for large rectal lesions. Initially conceived for treating benign lesions, its indications were extended to early rectal cancer treatment when Hermanek and Gall [1] assessed criteria to determine lesions at "low risk" for recurrence. One increasingly recognized advantage of the technique versus standard transanal surgery is the high rate of en bloc resection with disease-free margins, which is strictly related to the risk of recurrence [2].

With the advent of endoscopic submucosal dissection (ESD) about 10 years ago, flexible endoscopy permitted a surgical-like technique for en bloc resection of superficial lesions of the digestive tract. First indicated for the upper gastrointestinal tract [3], ESD then was applied to the lower gastrointestinal tract with promising results [4]. Although ESD represents an alternative to endoscopic mucosal resection (EMR) of the colon, its application to the rectum can be compared with TEM, both aiming to achieve en bloc R0 excision.

This study aimed to evaluate in a systematic review and meta-analysis whether ESD has clinically relevant short-term advantages in terms of safety and effectiveness compared with TEM in the treatment of large nonpedunculated rectal lesions preoperatively assessed as noninvasive.

Methods

The methods for the analysis and generation of inclusion criteria were based on the Cochrane Collaboration guidelines [5] and the PRISMA recommendations [6]. According to population, interventions, comparators, outcome measures, and setting (PICOS) criteria, patients were included if they had large nonpedunculated rectal lesions preoperatively assessed as noninvasive for which either TEM or ESD was indicated. The study methods were documented in a protocol registered and accessible at http://www.crd.york.ac.uk/prospero/ (Registration no. CRD42012001882).

Criteria for identifying studies and eligibility

The study aimed to include randomized or quasi-randomized studies that directly compared TEM and ESD. Because we knew and verified that similar studies were not available, we included prospective series that examined one of the two treatments provided they had the same inclusion and exclusion criteria. To be eligible, studies had to include reports on patients with a large (>2 cm) nonpedunculated rectal lesion preoperatively assessed as noninvasive by digital examination and/or endoscopic ultrasound (EUS) (confined to the mucosal layer) or lesions treated endoscopically by the ability to be lifted when the submucosal layer was injected below the lesion.

The exclusion criteria ruled out preoperative biopsies positive for invasive malignancy when available, TEM performed in a non-full-thickness fashion, and the impossibility to hive-off data from mixed series. Also excluded were studies reporting data on colon and rectal lesions that could not be broken up.

The criteria required that TEM had been performed in full-thickness fashion according to the technique described by Buess et al. [7]. When the technique was not specified, the authors were contacted for confirmation. Articles were included if a submucosal dissection was performed by TEM only for those lesions at risk for peritoneal opening. The criteria required that ESD had been performed after submucosal injection and lifting by any of the techniques described in the literature, including the different knives available.

Because most of the ESD series merged data on colonic and rectal lesions in a way that the two types could not be distinguished, the authors were contacted to provide a database of their published series restricted to rectal lesions only. Rectal lesions were defined as any lesion with an upper margin located within 18 cm of the anal verge, which was assessed by means of rigid rectoscopy in the TEM series and by flexible endoscopy in the ESD series.

End points

The primary end point of this review was effectiveness of resection (i.e., en bloc resection rate, defined as the rate of lesions excised in a single specimen, and R0 resection rate,

defined as the rate of lesions excised with margins free of disease) as assessed by the pathologist. The secondary end points were size of the lesions excised, time for completion of the procedure, safety (i.e., postprocedural complications such as bleeding and perforation and the need for abdominal surgery to manage complications), recurrence rate as assessed by a minimum of 6 months follow-up evaluation, the need for abdominal surgery for oncologic reasons, and finally the overall need for abdominal surgery. Abdominal surgery was defined as any type of surgery performed through an abdominal access.

Search strategy

Searches of the published literature were conducted for the period between January 1984 and December 2010. Only articles published in English or German were included. Studies were identified by electronic searches of Pubmed and EMBASE.

The following strategy was used to search both PubMed and EMBASE at a single time during January 2011: endoscopic AND submucosal AND resection* OR (endoscopic AND submucosal AND dissection*) OR (endoscopic AND submucosal AND excision*) OR (endoscopic AND mucosal AND resection*) OR (endoscopic AND resection*) OR (endoscopic AND excision*) OR (endoscopic AND mucosal AND excision*) OR (endoscopic AND treatment*) OR (endoscopic AND therapy*) OR (rectoscopic AND mucosal AND resection*) OR (rectoscopic AND resection*) OR (rectoscopic AND excision*) OR (rectoscopic AND mucosal AND excision*) OR (rectoscopic AND treatment*) OR (rectoscopic AND therapy*) OR (colonoscopic AND mucosal AND excision*) OR (colonoscopic AND resection*) OR (colonoscopic AND excision*) OR (colonoscopic AND treatment*) OR (colonoscopic AND therapy*) AND (colorectal AND 'neoplasms'/exp OR (colorectal AND tumor*) OR (colorectal AND tumour*) OR (colorectal AND neoplasm*) OR ('rectal'/exp AND neoplasm*) OR ('adenoma'/exp AND ('rectum'/exp OR 'rectal'/exp OR colorectal))) OR (tem OR (transanal AND endoscopic AND 'microsurgery'/exp) AND 'surgery'/exp OR transanal OR peranal AND (colorectal AND 'neoplasms'/exp OR (colorectal AND tumor*) OR (colorectal AND tumour*) OR (colorectal AND neoplasm*) OR ('rectal'/exp AND neoplasm*) OR ('adenoma'/exp AND ('rectum'/exp OR 'rectal'/exp OR colorectal)))) AND 'rectal'/exp AND 'neoplasm'/exp AND ('endoscopy'/exp OR endoscopic OR 'microsurgery'/exp OR transanal OR mucosal OR 'resection'/exp) OR (endoscopic AND mucosal AND 'resection'/exp) OR (endoscopic AND submucosal AND 'dissection'/exp) AND [1984-2010]/py.

Study selection

Titles were screened by two authors (A.A. and M.V.) to exclude nonrelated publications. Studies were excluded if the interventions, as reported in the abstracts, clearly differed from ESD or TEM or did not focus on the colorectal area.

The full text of the remaining articles was read to determine whether they were eligible for inclusion in the review. Studies were excluded in which preoperatively assessed rectal cancers were treated. When the same data of a single research group were reported in multiple publications, only the study reporting on the largest cohort was included.

Data extraction was independently performed by the two reviewers using predefined data extraction forms. A third investigator (M.M.) arbitrated in the event that agreement was not reached.

From each report, the reviewers independently collected the following data when available: year of publication, prospective or retrospective study design, enrollment period, number of patients included, mean age, gender distribution, lesion location (colon/rectum), Kudo pit-pattern classification [8], EUS, type of device used, mean operating time, mean tumor size, complication rate, rate of surgery due to complications, histology (adenoma, carcinoma in situ, invasive cancer, carcinoid), rate of histologically verified en bloc resection, rate of histologically verified complete resection (R0), rate of surgery for oncologic reasons, follow-up evaluation, histologically demonstrated recurrence, and need of further treatment for disease recurrence.

Quality assessment

All the studies fulfilling the selection criteria for this review were assessed to determine methodologic quality and risk of bias. The following quality items were scored: study design, sequence generation, cohort size, lesion type before intervention, lesion size, incidence of invasive carcinomas at final histology, length of the follow-up period, and objective definition of outcome parameters (complications and recurrence).

Table 1 reports the individual scores of quality assessment items per study. Because the data on colonic and rectal lesions from most of the ESD series were merged in such a way that they could not be distinguished, the authors were asked to provide a database of their published series restricted to rectal lesions only.

Statistical analysis

All analyses were performed according to the original treatment allocation (intention-to-treat analysis). Fixed- and

Table 1 Individual scores of quality assessment items per study

Author	Year	Intervention	Study characteristics			Tumor characteristics	Outcome assessment: safety		Outcome assessment: effectiveness	
			n	Study design	Consecutive series	Mean (±SD) size of lesions (mm)	Complications reported	Objective definition of complication	Recurrences reported	Objective definition of recurrence
Fujishiro et al. [11]	2006	ESD	35	Unclear	Yes	26.2 ± 14.0	Yes	No	Yes	No
Onozato et al. [12]	2007	ESD	30	Retrospective	Yes	32.8 ± NA	Yes	No	Yes	No
Ohya et al. [13]	2009	ESD	45	Unclear	Yes	35.0 ± NA	Yes	No	No	No
Iizuka et al. [14]	2009	ESD	26	Retrospective	Unclear	36.0 ± 20.0	Yes	No	No	No
Uraoka et al. [15]	2010	ESD	37	Retrospective	Yes	NA	Yes	No	No	No
Ishii et al. [16]	2010	ESD	9	Retrospective	Unclear	34.0 ± 16.0	Yes	No	Yes	Yes
Takeuchi et al. [17]	2010	ESD	14	Prospective	Unclear	28.7 ± NA	Yes	No	No	No
Yoshida et al. [18]	2010	ESD	110	Unclear	Unclear	29.1 ± NA	Yes	No	No	No
Saito et al. [19]	2010	ESD	158	Prospective	Yes	35.0 ± 18.0	Yes	No	No	No
Fusaroli et al. [20]	2009	ESD	8	Unclear	Unclear	41.9 ± NA	Yes	No	No	No
Niimi et al. [21]	2010	ESD	64	Retrospective	Yes	28.9 ± NA	Yes	No	No	No
Said and Stippel [22]	1996	TEM	260	Retrospective	No	NA	Yes	No	Yes	Yes
Cocilovo et al. [23]	2003	TEM	56	Prospective	Unclear	49.0 ± 22.8	Yes	No	Yes	No
Langer et al. [24]	2003	TEM	79	Retrospective	No	33.0 ± 15.0	Yes	No	Yes	No
Neary et al. [25]	2003	TEM	21	Prospective	Yes	39.0 ± 26.0	Yes	No	Yes	No
Schafer et al. [26]	2006	TEM	33	Retrospective	Unclear	91.2 ± 22.8	Yes	No	Yes	No
Ganai et al. [27]	2006	TEM	134	Retrospective	Unclear	31.0 ± 14.0	Yes	No	Yes	Yes
Doornebosch et al. [28]	2008	TEM	47	Prospective	Yes	44.7 ± 13.3	Yes	Unclear	Yes	No
Guerrieri et al. [29]	2010	TEM	402	Retrospective	Unclear	NA	Yes	No	Yes	No
De Graaf et al. [30]	2011	TEM	216	Prospective	Unclear	30.0 ± NA	Yes	No	Yes	Yes
Morino et al. [31]	2011	TEM	293	Prospective	Unclear	50.0 ± NA	Yes	No	Yes	No

ESD endoscopic submucosal dissection, *NA* not available, *TEM* transanal endoscopic microsurgery

random-effects meta-analyses of studies reporting single proportions were used to calculate an overall proportion. Because all the studies reported the results of only one technique in a series of patients, the logit transformed proportion of patients with recurrence or complication was used as the outcome parameter in the meta-analysis. We added 0.5 to all the cell frequencies of studies with a zero cell count.

Particularly, the random-effects model incorporates any remaining variability beyond chance that exists among studies, taking into account differences in sample size whereby proportions have been measured in each trial. This within-study variation was accounted for by using the exact binomial distribution. Individual and pooled estimates of these proportions together with 95 % confidence intervals (95 % CI) on recurrence and complication rates then were presented in the forest plots.

Operating time and tumor size were compared using their reported means and standard deviations (SDs). When means and/or SDs were not reported, they were estimated from the reported medians and ranges using the Hozo et al. [9] approach.

Potential sources of heterogeneity were explored in three different sensitivity analyses: fixed versus random-effects models (with the second model incorporating heterogeneity), cumulative meta-analysis (sequential inclusion of studies by date of publication), and influence meta-analysis (calculation of pooled estimates with omission of one study at a time).

All analyses were performed using R 2.15.0 and Meta-analyst 3.13 (for continuous outcomes) (R Foundation for Statistical Computing, Vienna, Austria) [10].

Results

The search retrieved 9,315 studies. The selection procedure is illustrated in Fig. 1. Of the 9,315 studies, 57 were

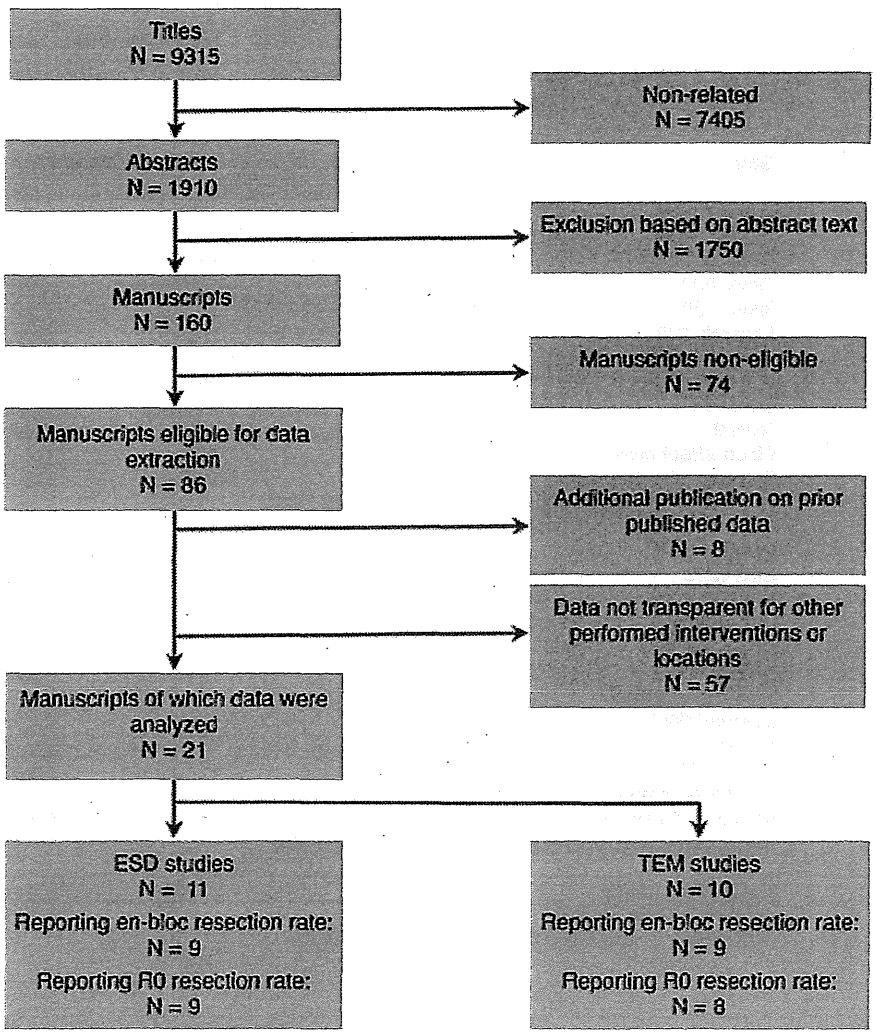

Fig. 1 Flow chart diagram of the systematic search and study selection strategy

excluded because it was unclear whether full-thickness TEM procedures were performed and whether an ESD procedure was performed to treat colonic or rectal lesions. We were unable to clarify these doubts because we received no reply to our request from the respective study authors. In all, 21 studies met the inclusion criteria for a total of 2,077 patients: 11 ESD series [11–21] totaling 536 patients, and 10 TEM series [2, 22–30], totaling 1,541 patients.

The mean polyp size was 35 mm (95 % CI 31–39 mm) in the ESD series versus 40 mm (95 % CI 29–51 mm) in the TEM series ($P = 0.393$). The operating time was 96 min (95 % CI 84–107 min) in the ESD series versus 67 min (95 % CI 53–82 min) in the TEM series ($P = 0.003$).

En bloc and RO resection

The en bloc resection rate was available for 9 ESD and 9 TEM series. The pooled estimate of the proportion of patients was 87.8 % (95 % CI 84.3–90.6 %) in the ESD series and 98.7 % (95 % CI 97.4–99.3 %) in the TEM series ($P < 0.001$, Fig. 2). Heterogeneity was greater in the ESD series ($I^2 = 60.1$ %) than in the TEM series ($I^2 = 46.4$ %).

The cumulative meta-analysis of all 18 studies showed a progressive increase from 81.4 to 95.1 % in the proportion of patients undergoing en bloc resection. The same proportion was quite constant (94.3–95.8 %), with no study strongly affecting the results in the influential, leave-one-out meta-analysis.

The R0 resection rate was available for 9 ESD and 8 TEM series. The pooled estimate of the proportion of patients was 74.6 % (95 % CI 70.4–78.4 %) in the ESD series and 88.5 % (95 % CI 85.9–90.6 %) in the TEM series ($P < 0.001$, Fig. 3). Heterogeneity was lower in the ESD series ($I^2 = 52.9$ %) than in the TEM series ($I^2 = 69.1$ %). The cumulative meta-analysis of all 17 studies showed a progressive increase from 62.9 to 82.7 % in the proportion of patients undergoing R0 resection. Again, the same proportion was quite constant (81.4–83.7 %) in the influential meta-analysis.

Perioperative complications

Data regarding perioperative complications were retrieved for all 11 ESD series and 8 of the TEM series. Altogether,

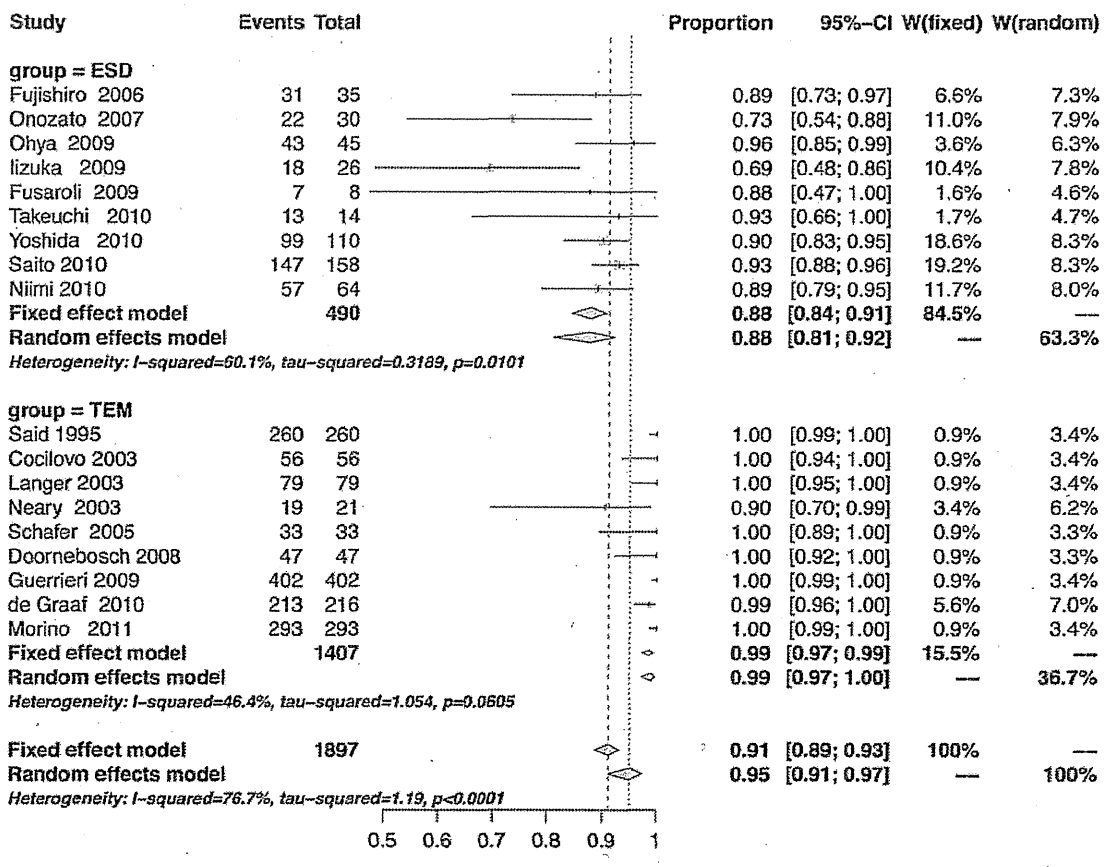

Fig. 2 En bloc resection rates for ESD and TEM, showing a statistically significant advantage of TEM ($P < 0.001$)

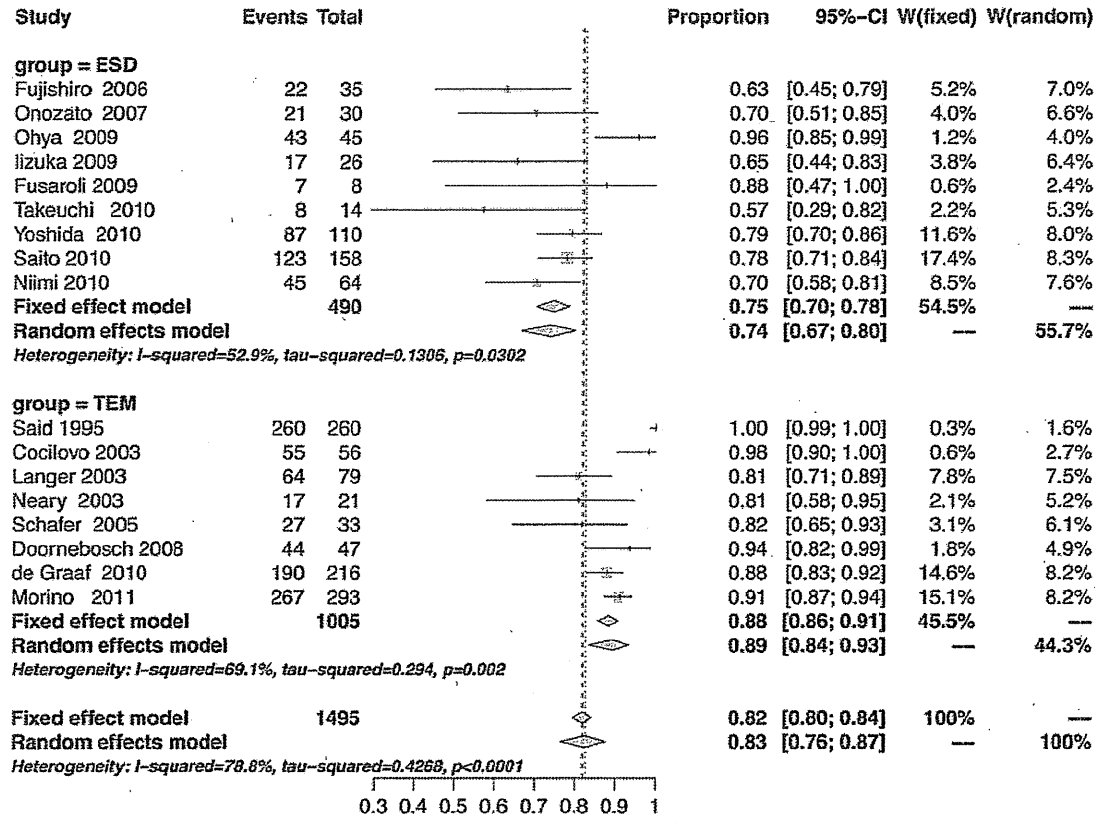

Fig. 3 R0 resection rates for ESD and TEM, showing a statistically significant advantage of TEM ($P < 0.001$)

1,887 patients (536 ESD and 1,351 TEM patients) were included in the analysis of complications. The complications after ESD were rectal bleeding ($n = 19$) and perforation ($n = 20$). The complications after TEM were suture leakage ($n = 43$), rectal bleeding ($n = 30$), fistulas ($n = 7$), urinary infection or retention ($n = 6$), and others ($n = 11$).

The proportion of patients with complications was 8.0 % (95 % CI 5.4–11.8 %) after ESD versus 8.4 % (95 % CI 5.2–13.4 %) after TEM (P = 0.874, Fig. 4). Heterogeneity was low in the ESD series ($I^2 = 25.0$ %) but extreme by comparison in the TEM series ($I^2 = 80.5$ %). A cumulative meta-analysis of all 19 studies showed a progressive increase from 4.2 to 8.6 % in the proportion of patients with complications. This proportion ranged from 7.1 to 8.7 %, without any single-trial effect, in the influential meta-analysis.

The pooled proportion of patients with perioperative events requiring additional abdominal surgery for complication control was 1.3 % (95 % CI 0.5–3.3 %) in the ESD series and 1.6 % (95 % CI 1.0–2.6 %) in the TEM series ($P = 0.665$, Fig. 5). Heterogeneity was absent in the ESD series ($I^2 = 0.0$ %) and low in the TEM series ($I^2 = 14.4$ %). A cumulative meta-analysis showed that 1.1–2.1 % of the patients required additional abdominal surgery. The influential meta-analysis showed a range of 1.3–1.7 %.

Histology

Only nine ESD and eight TEM series provided histology data. In all, 1,929 patients (488 ESD and 1,441 TEM patients) were included in the analyses of histology. Final pathology demonstrated an adenoma in 156 ESD patients (31.9 %) and 1,278 TEM patients (89.1 %), pTis or pT1sm1 cancers in 279 ESD patients (57.1 %) and 79 TEM patients (5.5 %), and invasive adenocarcinoma (pT1sm2 or more) in 45 ESD patients (9.2 %) and 73 TEM patients (5.1 %). Eight patients in the ESD group and four in the TEM group had another diagnosis.

The pooled estimate of the proportion of patients with invasive adenocarcinoma was 9.5 % (95 % CI 5.7–15.5 %) in the ESD series and 3.9 % (95 % CI 1.5–9.7 %) in the TEM series ($P = 0.095$). Heterogeneity was moderate in the ESD series ($I^2 = 50.7$ %) but extreme in the TEM series ($I^2 = 88.2$ %). The cumulative meta-analysis showed that 6.7–11.5 % of the patients required additional abdominal surgery. The influential meta-analysis showed a range of 5.0–7.8 %.

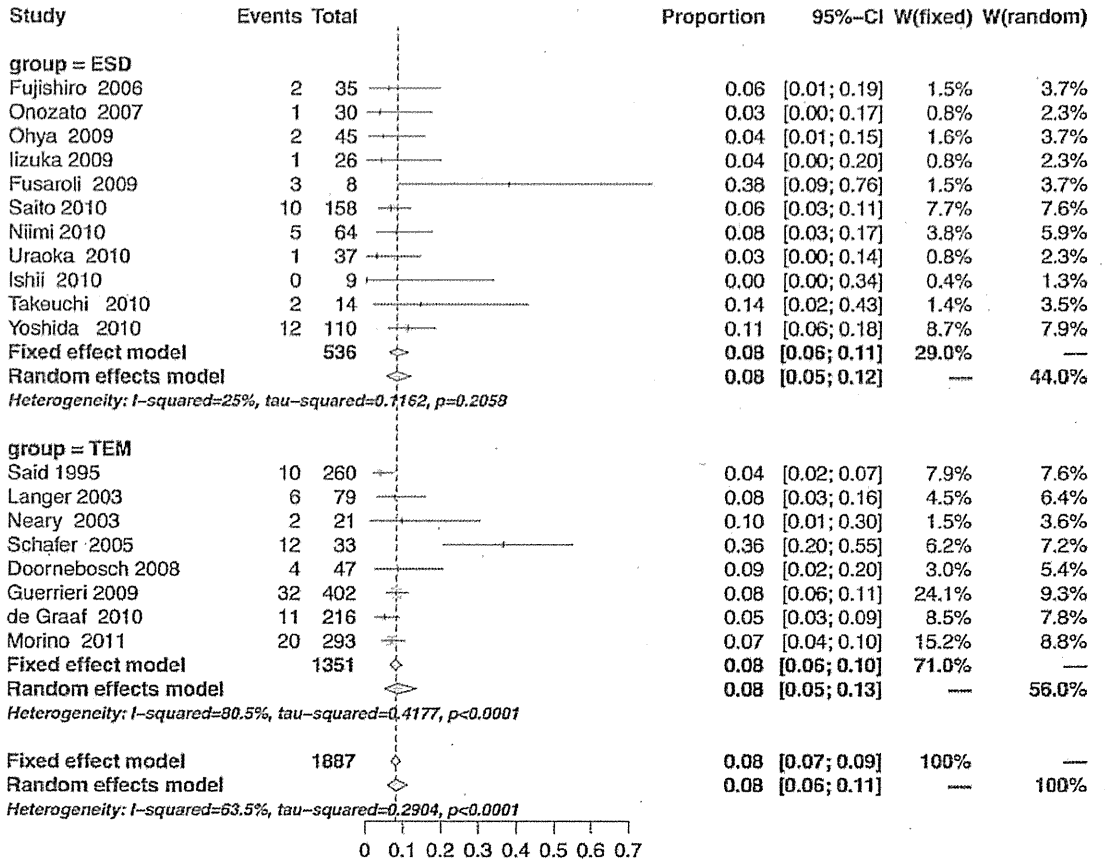

Fig. 4 Perioperative complication rates after ESD and TEM, showing substantial equivalence between the two groups ($P = 0.874$)

Recurrences and oncologic criteria

Only seven ESD series and nine TEM series provided recurrence data. All the ESD series reported a follow-up period of 6–12 months, whereas the TEM series reported an average follow-up period of 58.9 months (range, 1–204 months). In all, 1,811 patients (404 ESD and 1407 TEM patients) were included in the analyses of recurrences. The pooled estimate of the proportion of patients with adenoma recurrence was 2.6 % (95 % CI 1.3–5.2 %) in the ESD series and 5.2 % (95 % CI 4.0–6.9 %) in the TEM series ($P = 0.068$).

Heterogeneity was absent in the ESD series ($I^2 = 0.0$ %) and low in the TEM series ($I^2 = 21.5$ %). The pooled proportion of patients with perioperative events requiring additional abdominal surgery for oncologic indications or recurrence was 8.4 % (95 % CI 4.9–13.9 %) in the ESD series and 2.9 % (95 % CI 1.5–5.4 %) in the TEM series ($P = 0.011$). Heterogeneity was moderate in the ESD series ($I^2 = 40.2$ %) and greater in the TEM series ($I^2 = 63.3$ %).

Need for abdominal surgery

Data regarding the overall need for abdominal surgery, defined as any type of surgery performed through an abdominal access, were retrieved for eight ESD and nine TEM series. This included treatment of complications, recurrence, or major surgery for oncologic curative resection, as reported earlier. In all, 1,862 patients (455 ESD and 1407 TEM patients) were included in the analysis. The pooled estimate of the proportion of patients requiring abdominal surgery was 8.4 % (95 % CI 4.9–13.9 %) in the ESD series and 1.8 % (95 % CI 0.8–3.7 %) in the TEM series ($P < 0.001$, Fig. 6). Heterogeneity was moderate in both the ESD ($I^2 = 40.2$ %) and TEM ($I^2 = 48.1$ %) series.

Discussion

One of the most important risk factors for recurrence of rectal lesions is an R1 resection [2, 31, 32], which is

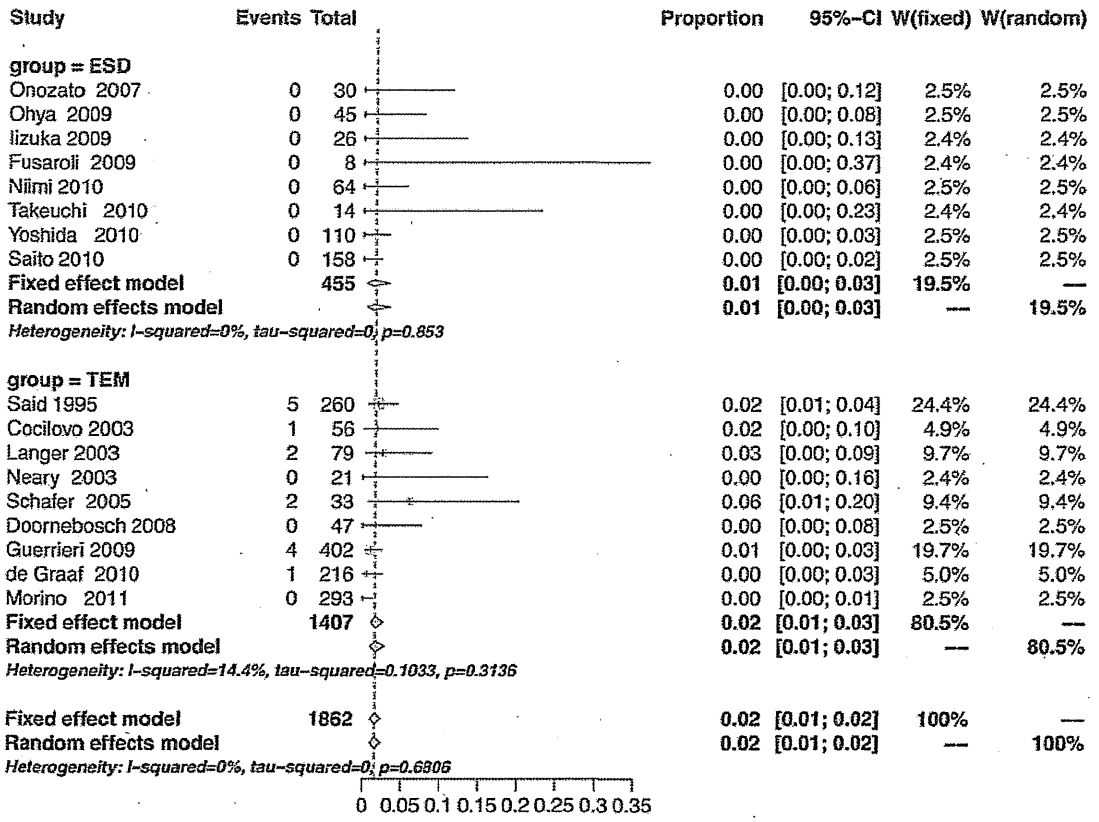

Fig. 5 Need for additional abdominal surgery for control of complications after ESD and TEM, showing a substantial equivalence between the two groups ($P = 0.665$)

obviously less probable when an en bloc resection is attempted. A recent systematic review by Barendse et al. [33] reported a recurrence rate of 11.2 % at 3 months after piecemeal EMR for colorectal lesions, which dropped to 1.5 % at 3 months after further endoscopic treatment. The authors claimed that this demonstrated the equivalence of EMR and TEM. However, the analysis contained a number of flaws. The two major flaws were that (1) all but one endoscopic series included only benign lesions, which suggested an evident selection of cases based on postoperative histology, and that (2) most of the TEM series included cases managed by a partial wall excision rather than a full-thickness technique, as suggested by most expert authors [29].

Due to the high rate of preoperatively misdiagnosed malignancies, piecemeal resection, as obtained by EMR, should not be performed when valid alternatives are available. Currently, surgeons performing endoscopic resection of a noninvasive rectal lesion should aim to use an ESD technique. Although rectal lesions currently are diagnosed earlier than in the past and can be treated with a variety of different techniques, we found no randomized or quasi-randomized study comparing ESD with TEM. Furthermore, although a meta-analysis of only randomized controlled trials would be ideal, case series data are the only evidence available to date.

The major limitation in the meta-analysis of the aforementioned data was the potential confounding by a systematic difference in patient characteristics between the two groups. In fact, although patients eligible for ESD will necessarily be assessed as having a superficial lesion, TEM often is performed also for those with an invasive lesion and almost always as a full-thickness excision. For this reason, we defined strict inclusion criteria that required a rectal lesion larger than 2 cm in diameter preoperatively assessed as a superficial neoplasm. By defining strict inclusion criteria, we excluded all TEM series that included preoperatively assessed malignant lesions because they were most probably biased by an extension of the inclusion criteria. The size limit requiring that lesions be larger than 2 cm was set according to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines [34], which aims to achieve en bloc resection with no fragmentation.

With these restrictions in selection, heterogeneity of the results was kept within a reasonable frame, although some of the study samples included in this analysis were relatively small. We also performed additional analyses to adjust for these potential confounders, which indicated that

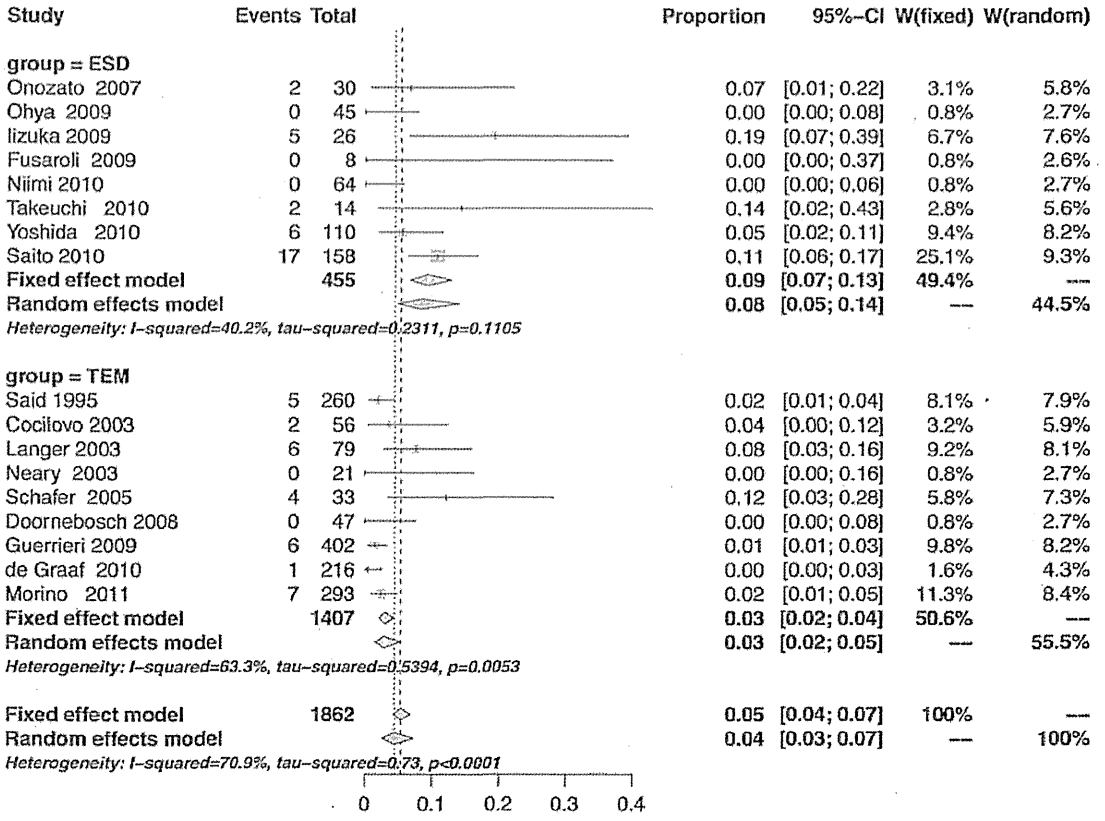

Fig. 6 Proportions of patients requiring abdominal surgery in the ESD and TEM series, showing a statistically significant lower incidence after TEM ($P < 0.001$)

their impact was null. By restricting the analysis to rectal lesions, we sought to limit any biases related to anatomic situations, which can influence the handling of lesions due to endoscope maneuverability restricted proximally to the rectum. As a consequence, the sensitivity analyses showed that no study had an influential effect on relative risk in the whole time frame.

A previous study comparing ESD with transanal excision (TAE) showed an advantage of ESD with respect to higher achievement of R0 en bloc resections [35]. Nonetheless, it is known that TEM is superior to TAE for the same reason, resulting in a significantly higher recurrence-free survival [36].

The TEM procedure remains the gold standard surgical treatment for rectal local excision. The pooled results of the current systematic review indicate that ESD for nonpedunculated superficial lesions of the rectum larger than 2 cm in diameter appears to be less effective than TEM, with an en bloc resection achieved for 88 % of patients compared with 99 % for TEM. Even more significantly, an R0 resection was achieved for 74 % of patients using ESD compared with 89 % using TEM. This difference was statistically significant. The apparently lower risk of recurrence shown in the ESD group was in fact not statistically significant, and in any case probably was due to the shorter follow-up period reported for the ESD series.

The ESD procedure is technically demanding with the currently available equipment and requires a significantly longer time to be completed. Yet the perioperative complication rate compared favorably with that of the TEM series, and the rate of abdominal surgery controlling complications was negligible.

Postoperative histology assessment demonstrated a much higher incidence of adenocarcinoma in the ESD series, which was attributable to a different way of classifying intramucosal lesions [37]. The rates of unpredicted invasive cancers treated in the two groups were comparable, but this required further surgery for oncologic reasons about four times more often in the ESD group due to the higher incidence of R1 resections than in the TEM group. In fact, a positive vertical margin after endoscopic resection is considered to be an indication for intestinal resection with lymph node dissection [34].

The high rate of further surgery for oncologic reasons after ESD also may explain the reduced risk of recurrence in this group. Although this could not be assessed through

the analysis of the selected papers, the reduced incidence of abdominal surgery after TEM might be due to the fact that patients with a cancer extended to the submucosal layer who received an R0 full-thickness resection often refused to undergo intestinal resection with lymph node dissection due to the limited risk of metastasis.

An indisputable advantage of ESD for rectal lesions is that it does not entail the need for general anesthesia or a prolonged hospital stay, as usually is the case after full-thickness TEM resection, although this more often is a trend or based on a difference in the practice of surgeons and endoscopists. On the other hand, TEM supporters could argue that preoperative assessment of benign or noninvasive lesions still is suboptimal, so that even in this analysis, a consistent number of cases actually resulted in malignancy.

The intraoperative finding of deep wall invasion misdiagnosed preoperatively can significantly influence oncologic outcome. Moreover, the risk for infiltration of the vertical margin is the only risk factor for recurrence and the reason why EMR should be avoided in such circumstances [34]. Of extreme interest would have been the influence on anal continence and rectal function, sexual and urinary dysfunction, and quality of life, but the lack of sufficient data on these issues precluded further analyses.

Based on the evidence of the current review and analysis, we can conclude that TEM achieves a higher rate of en bloc and R0 excision. As a consequence, full-thickness rectal wall excision by TEM significantly reduces the need for further abdominal treatment. How these results will ultimately translate into common daily clinical practice remains unclear. No randomized head-to-head comparisons between TEM and ESD have been performed to date. Our review clearly highlights the need for a large randomized study to obtain unbiased results on the effectiveness and safety of these two strategies for patients with large rectal lesions preoperatively assessed as adenomas or noninvasive neoplasms.

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Colorectal ESD

Current Indications and Latest Technical Advances

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KEYWORDS

- Endoscopic submucosal dissection (ESD) • Endoscopic mucosal resection (EMR)
- Endoscopic piecemeal mucosal resection (EPMR) • Colorectum
- Laterally spreading tumor granular type (LST-G)
- Laterally spreading tumor non-granular type (LST-NG)

KEY POINTS

- Endoscopic submucosal dissection (ESD) is a safe and effective procedure for treating colorectal laterally spreading tumors nongranular type (LST-NGs) larger than 20 mm, laterally spreading tumors granular type (LST-Gs) larger than 30 mm, 0-IIc lesions larger than 20 mm, intramucosal tumors with nonlifting sign, and large sessile lesions, which are all difficult to resect en bloc using conventional EMR, providing a higher en bloc resection rate as well as being less invasive than surgery.
- Establishment of a systematic training program for technically more difficult colorectal ESD in addition to further development and refinement of ESD-related instruments, devices, equipment, and injection solutions will help facilitate increased use of colorectal ESD throughout the world.

INTRODUCTION

Surgery had been the only available treatment for large colorectal tumors, even those detected at an early stage. In Japan, endoscopic mucosal resection (EMR)[1–5] is indicated for the treatment of colorectal adenomas, and intramucosal and submucosal superficial (SM1; invasion <1000 μm from the muscularis mucosae) cancers because of the negligible risk of lymph node (LN) metastasis[6] and excellent clinical outcome results.[2–4]

The endoscopic submucosal dissection (ESD) procedure is accepted as a standard minimally invasive treatment for early gastric and esophageal cancers in Japan.[7,8] Yamamoto and colleagues[9] and Fujishiro, Yahagi and colleagues and colleagues[10]

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first started performing colorectal ESDs in the early 2000s, but such procedures were being conducted by only a limited number of specialists. Because of the widespread acceptance of gastric and esophageal ESDs, the number of medical facilities that perform colorectal ESDs has been growing, and the effectiveness of colorectal ESD has been increasingly reported in recent years.[11–15]

Until the spring of 2012, colorectal ESDs had been performed in Japan in accordance with advanced medical treatment system No. 78 approved by the Japanese Ministry of Health, Labor, and Welfare in 2009, which distinguishes colorectal ESD from gastric and esophageal ESDs because of its greater technical difficulty.[15] The indications for colorectal ESD under this system were defined as (1) early colorectal cancers larger than 20 mm difficult to treat en bloc by EMR; and (2) adenomas with nonlifting sign or residual tumors larger than 10 mm difficult to treat by EMR.[16]

All candidate lesions for ESD had to be confirmed as being an intramucosal tumor using magnification colonoscopy[16–18] or endoscopic ultrasonography (EUS) before performing the procedure. More than 150 institutions had started performing colorectal ESDs in accordance with the advanced medical treatment system by using recent improvements in ESD-related instruments and devices, as well as various other technical innovations. In fact, a total of 3006 colorectal ESDs were performed in 143 institutions during a recent 1-year period using this advanced medical treatment system. Based on the reported excellent clinical results of colorectal ESDs in Japan, the Japanese health care insurance system has approved colorectal ESD for coverage and set the cost at 183,700 Japanese yen, which is approximately 3 times higher than the cost for conventional EMR. However, most patients younger than 75 years receive a 70% reduction in the treatment cost under the universal health insurance system in Japan.[15]

INDICATIONS FOR COLORECTAL ESD

The indications for colorectal ESD approved by the Japanese government's medical insurance system are colorectal adenomas and cancers with a maximum tumor size of 2 to 5 cm, taking into account the procedure's technical standardization and safety throughout Japan at the present time (**Table 1**).

Based on our previous clinicopathological analyses of laterally spreading tumors (LSTs),[5,16] LST nongranular type (LST-NGs) lesions have a higher rate of submucosal (SM) invasion, which can be difficult to predict endoscopically. Approximately 30% of LST-NGs with SM invasion are multifocal and such invasions are primarily SM superficial (SM1), which is especially difficult to predict before endoscopic treatment. LST-granular type (LST-Gs) lesions have a lower rate of SM invasion and most such invasions are found under the largest nodule or depression and are easier to predict endoscopically.[5,17] LST-Gs larger than 20 mm can be treated by planning endoscopic piecemeal mucosal resection (EPMR) rather than ESD, with the area having the largest nodule resected first before resection of the remaining tumor. LST-Gs larger than 30 mm are possible candidates for ESD, however, because they have a higher SM invasion rate and are more difficult to treat even by EPMR. Consequently, they are treated by either EPMR or ESD depending on the individual endoscopist's judgment.

The 0-IIc lesions larger than 20 mm, intramucosal tumors with nonlifting sign, and large sessile lesions, all of which are difficult to resect en bloc by conventional EMR, are also potential candidates for colorectal ESD.

Residual and recurrent tumors can be treated by ESD depending on the circumstances; however, such lesions usually involve severe fibrosis so they are not good candidates, except in the lower rectum, where the risk of perforation is very low.[17]

Table 1
Indications for colorectal ESD at National Cancer Center Hospital

Noninvasive Pattern Should be Diagnosed by Chromo-magnification Colonoscopy				
Tumor size, mm	<10	≥10–<20	≥20–<30	≥30
0-IIa, IIc, IIa + IIc (LST-NG)[a]	EMR	EMR	ESD	ESD
0-Is + IIa (LST-G)[b]	EMR	EMR	EMR	ESD
0-Is (villous)[c]	EMR	EMR	EMR	ESD
Intramucosal tumor with nonlifting sign[d]	EMR	EMR/ESD	ESD	ESD
Rectal carcinoid tumor[e]	EMR	ESD/Surgery	Surgery	Surgery

Noninvasive pattern diagnosed by chromo-magnification colonoscopy.

Abbreviations: EMR, endoscopic mucosal resection; EPMR, endoscopic piecemeal mucosal resection; ESD, endoscopic submucosal dissection; LST-G, laterally spreading tumor granular type; LST-NG, laterally spreading tumor nongranular type.

[a] 0-IIa, IIc, IIa + IIc (LST-NGs) >20 mm.

[b] 0-Is + IIa (LST-G) >30 mm.

[c] 0-Is (villous) >30 mm.

[d] Intramucosal tumors with nonlifting sign that are difficult to resect en bloc by conventional EMR. Residual and recurrent tumors can be treated by ESD depending on the circumstances; however, such lesions usually involve severe fibrosis so they are not good candidates except in the lower rectum where the perforation risk is very low.

[e] Rectal carcinoid tumors <1 cm in diameter can be treated by endoscopic submucosal resection using a ligation device simply, safely, and effectively, so not an indication for ESD.

Rectal carcinoid tumors smaller than 1 cm in diameter can be treated by endoscopic submucosal resection using a ligation device safely, effectively, and easily, so are not an indication for ESD.[18,19]

ESTIMATING DEPTH OF INVASION

A noninvasive pattern[20,21] and Sano Type II or IIIA capillary pattern (**Fig. 1**C)[22,23] should be confirmed in each lesion (see **Fig. 1**A–D), indicating that the lesion is suitable for EMR or ESD with the estimated invasion depth being less than SM1. No biopsies are recommended before ESD because they can cause fibrosis and may interfere with SM lifting.

ESD PROCEDURE AT NATIONAL CANCER CENTER HOSPITAL

Materials

Endoscope system

The endoscope system included a water jet endoscope (PCF-Q260JI and GIF-Q260J; Olympus Medical Systems Corp, Tokyo, Japan) with a water jet pump system (OFP1; Olympus Medical Systems Corp) (see **Fig. 1**).

ESD knives

ESD knives included a ball-tip bipolar needle knife with water jet function (Jet B-knife) (XEMEX Co, Tokyo, Japan) and a newly developed insulation-tipped electrosurgical knife (IT knife nano) (KD-612Q; Olympus Optical Co, Tokyo, Japan), in which the insulation-tip is smaller and the short-blade is designed as a small disk to reduce the burning effect on the muscle layer.

Distal attachment

Distal attachment was an ST hood short-type (DH-28GR and 29CR; Fujifilm Medical Co, Tokyo, Japan).

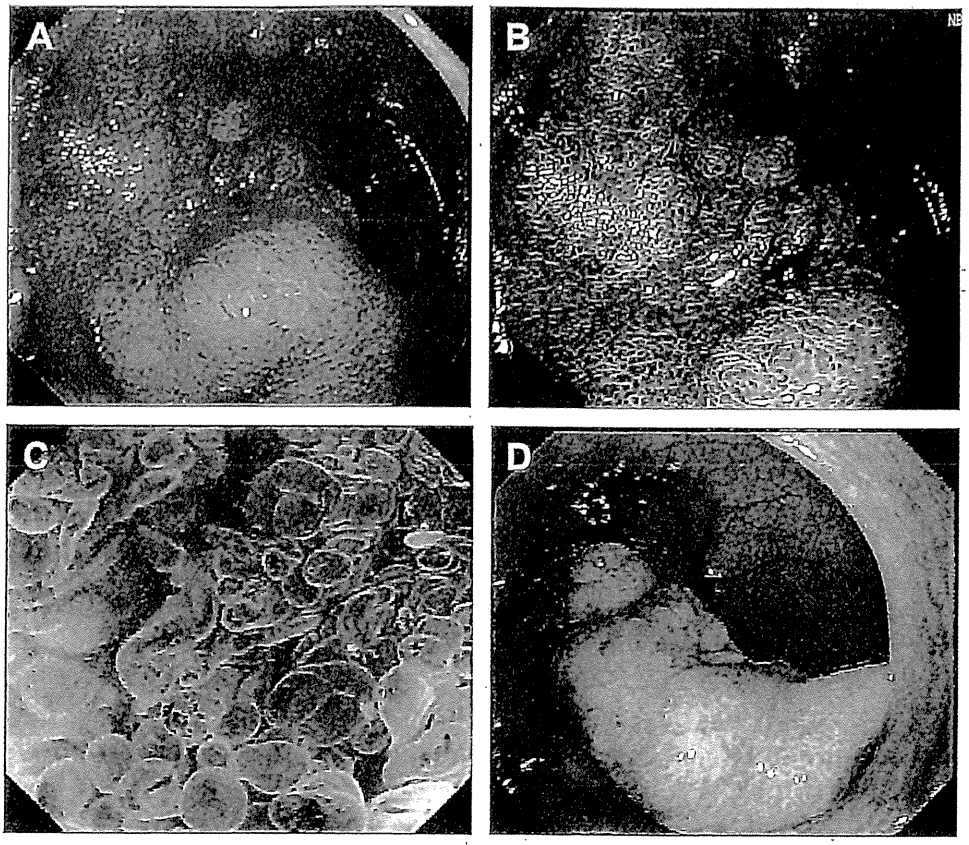

Fig. 1. ESD procedure. (*A, B*) LST-G–type lesion 100 mm in size located in upper rectum (white light image in *A* and narrow band imaging (NBI) image in *B*). (*C*) A noninvasive Sano Type IIIA capillary pattern was confirmed in this lesion, indicating that the lesion was suitable for ESD with the estimated invasion depth being less than SM1. No biopsies were performed before ESD because they could cause fibrosis and could interfere with SM lifting. (*D*) Lesion margins delineated before ESD using 0.4% indigo-carmine dye spraying.

Carbon dioxide regulator

The CO_2 regulator was a UCR (Olympus Medical Systems) or Gas Regulator, Crown (Model FR-IIS-P; Yutaka Engineering, Tokyo, Japan).[12,24]

Bipolar hemostatic forceps

The bipolar hemostatic forceps used were the HemoStat-Y forceps (H-S2518; Pentax Co, Tokyo, Japan).

Submucosal injection solution

Mixtures of 2 solutions were prepared before ESD to create a longer-lasting SM fluid cushion.

Solution 1: Indigo-carmine dye (2 mL of 1%) and epinephrine (1 mL of 0.1%) were mixed with 200 mL Glyceol (Glyceol, Chugai Pharmaceutical Co, Tokyo, Japan)[25] (10% glycerin and 5% fructose) in a container, and the solution was then drawn into a 5-mL disposable syringe.

Solution 2: MucoUp (MucoUp, Seikakagu Co, Tokyo, Japan)[9] was drawn into another 5-mL syringe.

During the actual ESD procedure, a small amount of solution 1 was injected into the SM layer first to confirm the appropriate SM layer elevation and then solution 2 was

injected into the properly elevated SM layer. Finally, a small amount of solution 1 was injected again to flush any residual amount of solution 2.

Electrosurgical generators

The electrosurgical generators were the VIO300D (**Table 2**) (ERBE, Tubingen, Germany) and ESG100 (Olympus Medical Co, Tokyo, Japan).

Colorectal ESD Procedures

The procedures were primarily performed using a Jet B-knife and an IT knife nano[21] with CO_2 insufflation[12,24] instead of air insufflation to reduce patient discomfort (see **Fig. 1**; **Fig. 2**). A short-type ST hood (see **Fig. 2**A, B) was used from the start of each colorectal ESD to creep into the narrow SM layer more easily and provide countertraction for the resected specimen.

After the colorectal ESD was completed, routine colonoscopic review to detect any possible perforation or exposed vessels was conducted (see **Fig. 2**C), and minimum coagulation was performed using the Hemostat-Y forceps on nonbleeding visible thick vessels to prevent postoperative bleeding. The resected specimen was stretched and fixed to a board using small pins (see **Fig. 2**D).

CLINICAL OUTCOMES OF ESDS AT NATIONAL CANCER CENTER HOSPITAL

The en bloc resection rate was 91% and the curative resection rate was 87% for 900 ESDs (**Table 3**). There were a total of 687 (76%) carcinomas; among them, 117 cases (13%) were diagnosed as SM deep and/or positive for lympho-vascular invasion, and additional surgery was recommended for most such noncurative cases. The median procedure time was 60 minutes with a mean of 100 minutes and the mean size of resected specimens was 40 mm (range 20–150 mm). The postoperative bleeding rate for colorectal ESD was 1.7% (15/900) and the perforation rate was 2.7% (24/900), but only one immediate and one delayed perforation required emergency surgery.

In our previously reported prospective multicenter study, multivariate analysis revealed that large tumor size (≥50 mm) and a lower experience level in which fewer

Table 2
The setting of VIO300D for colorectal endoscopic submucosal dissection at National Cancer Center Hospital

Device	Procedure	VIO300D
Jet B-knife	Mucosal cutting	Drycut effect 3, 80 W
	Submucosal dissection	Swift coagulation. Effect 2, 40 W
	Coagulation	Forced coagulation. Effect 2, 40 W
IT knife nano	Mucosal cutting	Drycut effect 3, 80 W
	Submucosal dissection	Swift coagulation. Effect 2, 40 W
	Coagulation	Forced coagulation. Effect 2, 40 W
Hemostat-Y	Coagulation	Bipolar soft effect 4, 25 W

The setting of VIO300D for colorectal endoscopic submucosal dissection at National Cancer Center Hospital.
Jet B-knife and IT knife nano
Drycut mode (80 W, effect 3) for marginal resection.
Forced coagulation mode or swift coagulation mode of 40 W, effect 2 for SM dissection.
Hemostat-Y
Bipolar soft mode (25 W, effect 4).

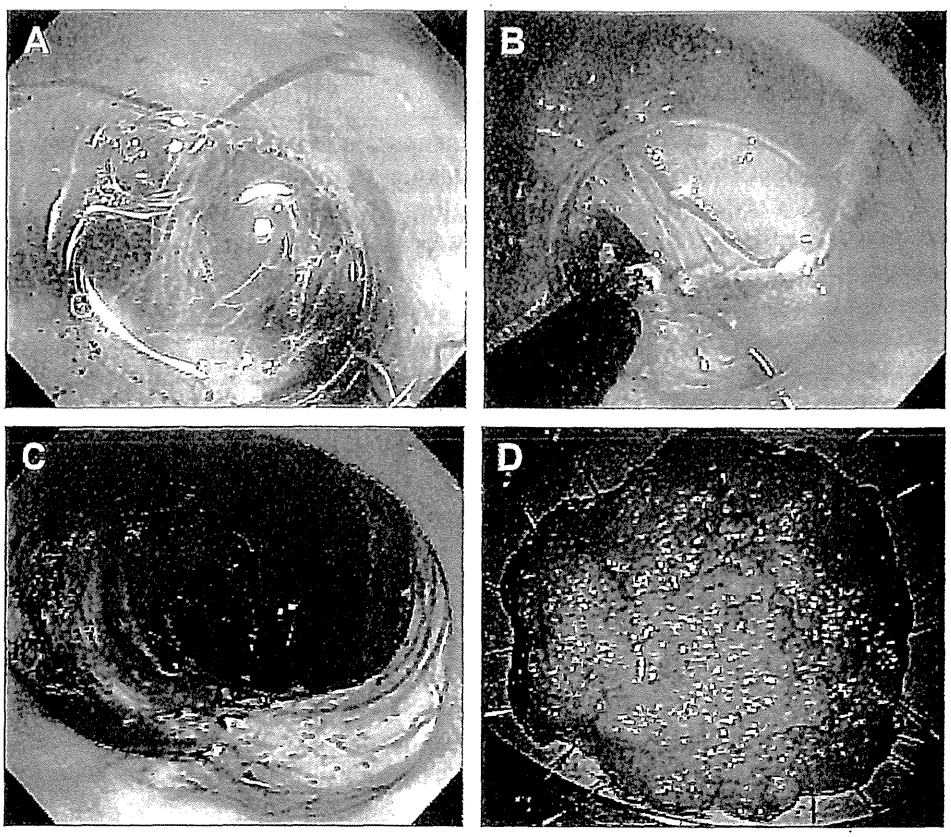

Fig. 2. ESD procedure. (*A*) An ST hood short-type was used from the start of each colorectal ESD to creep into the narrow SM layer more easily and provide countertraction for the resected specimen. Thick vessels could be visualized clearly, so precoagulation was necessary using Hemostat-Y before SM dissection. (*B*) Following injection of glycerol and sodium hyaluronate acid solution into the SM layer, SM dissection of lesion was performed by using the IT knife nano. (*C*) Ulcer bed after successful en bloc resection completed. (*D*) Resected specimen 100 × 80 mm in diameter with tumor-free margins. Histology revealed an intramucosal cancer and curative R0 resection was completed.

Table 3
Clinical results of colorectal ESDs at National Cancer Center Hospital

Years	2004–2012
No. of endoscopic submucosal dissections (n)	900
Tumor location Rectum/Total n (%)	238/900 (26%)
Age, y mean±SD	66 ± 10
Mean tumor size, mm mean±SD	37 ± 18
Mean procedure time, min (median) mean±SD, min. (median)	100 ± 70 (60)
En-bloc resections n/total (%)	728/900 (91%)
Snare use n/total (%)	203/900 (23%)
Cancer %	76%
Curative resections n/total (%)	783/900 (87%)
Perforations n (%)	24 (2.7%)
Delayed bleeding cases n (%)	15 (1.7%)

than 50 ESDs were performed were independent factors for a significantly increased risk of complications.[26]

TECHNICAL PROGRESS OF COLORECTAL ESD

Until recently, colorectal ESDs had been performed mainly in Japan,[9–15,24,26–29] because of the procedure's technical difficulty and because ESD is most frequently used to treat early gastric cancer, which is much more common in Japan than in Western countries,[30] although some trained endoscopists have started to do colorectal ESDs in other Asian countries, including South Korea,[15,31,32] as well as in Europe[33,34] and the United States.[35] One of our Japanese colleagues, Dr Norio Fukami, is now working in the United States in Colorado, routinely performing many successful ESDs,[36] but there is an issue of the limited availability of dedicated devices and solutions for safer ESD in the United States.

To reduce the perforation rate for colorectal ESD, the use of specialized knives,[7,8,27] distal attachments,[9] and hypertonic solutions (glycerol[25] and MucoUp[9]), which produce longer-lasting and higher SM elevation cushions, are necessary for safer ESDs because of the thinner colonic wall. The Jet B-knife is safer because electric current is limited to the needle, the bipolar system prevents electric current from passing to the muscle layer, and the new water-jet function with which SM injection is possible reduces the need for more frequent device changes.

ESD enables treatment of even recurrent lesions after incomplete endoscopic resections, as well as large colorectal LSTs (>10 cm in diameter), but such ESDs are still challenging even in an expert's hands.[26] It is important, therefore, to examine lesions carefully using chromo-magnification colonoscopy[19,20] and to diagnose them accurately before treatment, to reduce unnecessary noncurative resections of SM deep invasive cancers.[6]

Comparison Between ESD and EMR

The primary advantage of ESD compared with EMR is a higher en bloc resection rate for large colonic tumors that had been treated by surgery previously. Consequently, ESD has a lower recurrence rate compared with EMR (2% vs 14%), providing a better quality of life for patients compared with surgery.[37] Future studies should be designed to compare the clinical outcomes between ESD and surgery rather than between ESD and EMR, because the indications for ESD and EMR are different, as are the relevant tumor characteristics.

In the past, EPMR had been considered a feasible treatment for colorectal LSTs because of a low local recurrence rate for such tumors and repeat endoscopic resection was considered sufficient for most local recurrent tumors in Japan.[37,38] In Western countries, EPMR is still the gold standard treatment for LSTs larger than 20 mm in diameter.[39] In our case series,[37] EPMR also was effective in treating many LST-Gs 20 mm or larger, but 3 cases (1.3%) required surgery after such piecemeal resections, including 2 cases of invasive carcinoma recurrence. Based on our results, EPMR cases for LSTs 30 mm or larger should be considered for ESD or laparoscopic-assisted colorectal (LAC) surgery because of the increased risk of SM invasion and because accurate histologic evaluation is difficult in such cases.[16,37]

COMPARISON OF ESD AND SURGERY

LAC is one of the minimally invasive alternatives to open surgery for colorectal cancers, whereas ESD is another such alternative. Comparative effectiveness data on ESD versus LAC resection of early colorectal cancer has so far been unavailable,

although such information would be most enlightening given the considerable differences in the potential benefits and risks between the 2 procedures.

We compared ESD with LAC, therefore, as minimally invasive treatments for early colorectal cancer.[40] This comparison indicated that ESD was safe and provided an excellent prognosis despite different indications for ESD and LAC. In terms of the length of hospital stay and time to oral intake after the procedures, both periods were shorter for the ESD group than for the LAC group. ESD and LAC have quite different indications, however, so if the primary indications are a noninvasive colorectal lesion diagnosed preoperatively as intramucosal to SM1 (<1000 μm), the patient's quality of life following treatment for such an early colorectal cancer would probably be better with ESD.[40,41]

Although there have been some cases requiring additional surgical resection after endoscopic resection for SM invasive cancer,[41] colorectal ESD has succeeded in reducing avoidable surgery for mucosal carcinomas and improving the overall quality of life for most patients.

For rectal cancer treatment, however, a longer procedure time is required for LAC compared with ESD, and transanal resection is more invasive than ESD with a significantly higher recurrence rate.[42,43] Accordingly, ESD is the preferred choice for noninvasive rectal cancers.

POST-ESD CARE RECOMMENDATIONS

Supported by our comparative data analysis between ESD and EMR, follow-up endoscopy is recommended after 1 year for curative en bloc ESD cases and after 6 months for piecemeal ESD cases, considering local recurrence rates.[37,38] Even for pathologically curative resection cases, computed tomography (CT) or EUS examination is recommended for SM1 and piecemeal resection cases to detect LN metastasis or distant metastasis. Colonoscopy and a CT scan are scheduled every 12 months, whereas carcinoembryonic antigen (CEA) is checked every 6 months for at least 5 years at National Cancer Center Hospital (the authors' institution).

Surgery is recommended for SM2 or deeper invasion and when lymphovascular invasion or poorly differentiated cancer is diagnosed histologically.[6]

ESTABLISHMENT OF SYSTEMATIC TRAINING FOR COLORECTAL ESD

Probst and colleagues[34] reported that ESD performed in the distal colon is feasible with acceptable complication risks in a European setting. They also indicated resection rates were not as high as those reported in Japanese studies, although a clear learning curve was evident from their results.

Establishment of a systematic training program for technically more difficult colorectal ESD, together with further development and refinement of the instruments, devices, equipment, and injection solutions used in the procedure, are encouraged to facilitate increased use of colorectal ESD not only in Japan, but also in the rest of the world, where there is much less clinical experience in using ESD.[44]

SUMMARY

ESD is a safe and effective procedure for treating colorectal LST-NGs larger than 20 mm, LST-Gs larger than 30 mm, 0-IIc lesions larger than 20 mm, intramucosal tumors with nonlifting sign, and large sessile lesions, which are all difficult to resect en bloc using conventional EMR, providing a higher en bloc resection rate, as well as being less invasive than surgery. Establishment of a systematic training program for technically more difficult colorectal ESD in addition to further development and